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EDTA, propylene glycol, chlorhexidine

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(54) Title: PRESERVATIVE SYSTEM FOR OPHTHALMIC SOLUTIONS

(57) Abstract: Multi-use ophthalmic solutions require a preservative system designed to kill microbes that come in contact with the solution. Failure of the preservative system can pose potential ocular infection hazard to the solution user. Preservative systems must be both efficacious and non-irritating, a balance which is often difficult to achieve. The present invention describes a three-component preservative system for ophthalmic solutions which is both effective in preventing microbial growth and is compatible with the ocular environment.

REVISED VERSION

INTERNATIONAL SEARCH REPORT

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PCT/US00/27524

A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST/ USPAT, DERWENT, JPO, EPO;

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,046,706 A [KREZANOSKI et al] 6 SEPTEMBER 1977, entire document , especially col. 5, line 51 - col. 7, line 68.	1-20
Y	US 4,537,746 A [OGUNBIYI et al] 27 AUGUST 1985, entire document.	1-20
Y	US 4,354,952 A [RIEDHAMMER et al] 19 OCTOBER 1982, entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DERRICK G. HAMLIN DEBORAH THOMAS PARALEGAL SPECIALIST Telephone No. (703) 308-0651

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PRESERVATIVE SYSTEM FOR OPHTHALMIC SOLUTIONS

Description of **WO0124837**

PRESERVATIVE SYSTEM FOR OPHTHALMIC SOLUTIONS
FIELD OF THE INVENTION :
The present invention relates to ophthalmic solutions and more particularly to a composition for use with contact lenses and a method of treating the same.

BACKGROUNDOF THE INVENTION :
Ophthalmic solutions are commonly provided in multi-use bottles. These solutions are often instilled directly into the eye one or more times a day to either deliver medications or to relieve the symptoms of dry eye (artificial tears). On the other hand, contact lens solutions are utilized to soak, disinfect, clean and wet contact lenses.

These solutions are not instilled directly in the eye from the bottle, but do subsequently contact the eye when the lenses are
Ophthalmic solutions are provided sterile, but once opened, are susceptible to microbial contamination. In the case of multi-use solutions the formulation contains a preservative system designed to kill microbes that come in contact with the solution.

This protects the patient from infection due to the ophthalmic solution during the prescribed usage.

Traditionally, preservatives for ophthalmic solutions fall into one of two categories, alcohols and amine or ammonium containing compounds. Typical alcohol anti microbial agents include benzyl alcohol, phenethyl alcohol and chlorbutanol.

These alcohols have limited solubility in aqueous solution and tend no to be stable preservatives due to oxidation, evaporation and interaction with the plastic bottle.

More commonly, amine and ammonium compounds are utilized as anti microbial agents in ophthalmic solutions. Representative compounds in this category include benzalkonium chloride (BAK), chlorhexidine (CHG), polymeric biguanides and other polymeric amine and ammonium containing compounds.

Although the amine and ammonium containing compounds have acceptable anti microbial activity, and are used commercially to preserve ophthalmic solutions, there are significant disadvantages associated with these compounds. In particular, these compounds are often toxic to the sensitive tissues of the eye. For example, benzalkonium chloride (BAK) containing ophthalmic solutions are known to cause eye irritation in patients. Polymeric amine and ammonium compounds are less toxic than
BAK containing solutions but still can cause irritation responses in a significant number of patients. Chlorhexidine, on the other hand, has proven to be more biocompatible than the other amine and ammonium anti microbial agents and therefore non-irritating at the levels used. However, the mildness of chlorhexidine to the ocular environment is offset by the fact that chlorhexidine is a relatively weak preservative.

One attempt has been made to combine anti microbial agents and is described in
U. S. Pat. No. 5,453,435. The invention teaches the use of chlorhexidine in combination with a polymeric biguanide to achieve a broad spectrum anti microbial preservative system.

The challenge is to develop preservative systems for ophthalmic solution applications which not only have a wide spectrum of anti microbial activity, but which also are more biocompatible and therefore less irritating to the eye.

SUMMARY OF THE INVENTION :
The present invention relates to improved ophthalmic solutions which comprise an effectively anti microbial amount of a preservative system, wherein the preservative system comprises:
a. chlorhexidine or a water soluble salt thereof
b. propylene glycol

c. ethylenediaminetetraacetic acid and its salts
Additionally, the invention relates to methods of treating contact lenses, such as methods of disinfecting contact lenses, which employs an ophthalmic solution comprising the anti microbial preservative system.

DETAILED DESCRIPTION OF THE INVENTION:
Chlorhexidine (salts) has proven to be a biocompatible anti microbial agent for ophthalmic solutions, that is, it has minimal impact in the ocular environment. This beneficial feature of chlorhexidine is offset by its effectiveness as a preservative at the levels normally used in ophthalmic solutions. Simply increasing the concentration of chlorhexidine will improve its action as a preservative, but will reduce its mildness and increase its potential for ocular irritation. Because chlrohexidine is a broad spectrum anti microbial, it would be desirable to enhance its preservative action, yet retain its non-irritating characteristics.

It is an object of this invention to define a ternary preservative system that provides a margin of safety to the patient yet does not cause ocular irritation.

Another object of this invention is to provide ophthalmic solutions that will conform toFDA and ISO regulatory requirements for preservative efficacy.

It is a further object of this invention to provide improved preservative systems for contact lens solutions. The first component of the preservative system is a compound selected from the group consisting of chlorhexidine(1, 1'-hexamethylenebis [5- (p-chlorophenyl) biguanide]) and water soluble salts thereof. Suitable salts include the gluconate, acetate, glutamate, succinamate, monodiglycolate, dimethanesulfonate, lactate, diisobutyrate and glucoheptonanate salts. A preferred material is chlorhexidine gluconate (available from XTTRIUM Laboratories, Inc.,
Chicago, IL (U. S. A.).

The second component of the preservative system is propylene glycol, a compound that has been utilized in ophthalmic solutions and is recognized to be safe up to at least 1.0% in ophthalmic solutions.

The third component is a sequestering agent (or chelating agent) normally used in ophthalmic solutions at levels from about 0.025 to about 2.0 weight percent. It should be noted that at the higher concentrations the sequestering agent may cause ocular irritation. Examples of preferred sequestering agents include ethylenediaminetetraacetic acid (EDTA) and its salts with the disodium salt (disodium edetate) being especially preferred.

Applicants have discovered that the preservative system of this invention provides desired anti microbial efficacy with concomitant ocular biocompatibility.

Ophthalmic solutions can be formulated with the preservative system of this invention to achieve both safety and efficacy.

The preservative system of this invention is employed in ophthalmic solutions in an anti microbially effective amount.

As used herein, the term"ophthalmic solution"denotes an aqueous solution intended for application in the eye, including solutions for the care of contact lenses.

Contact lens solutions include solutions for the care of conventional soft hydrogel lenses, silicone hydrogel lenses and hard lenses, including rigid gas permeable (RGP) lenses.

Such solutions for the care of contact lenses include saline solutions, cleaning solutions, enzyme solutions, disinfecting solutions, conditioning solutions, soaking solutions, rinsing solutions and combination (multi purpose) solutions.

Theterm"preservative"or"preservative system"denotes the agents included in the ophthalmic solutions for the purpose of inhibiting the growth of microorganisms in the product, thereby helping to maintain sterility during use. Additionally, the term "anti microbial agent"is used herein to denote a specific active agent which provides the anti microbial efficacy.

The term"anti microbially effective amount"denotes an amount which is effective to at least inhibit growth of microorganisms in the solution. Preferably, the amount of anti microbial agents is sufficient to disinfect

the solution by killing microorganisms therein according to international preservative efficacy requirements for ophthalmic solutions, includingFDA and ISO requirements.

Generally, the ophthalmic solutions of this invention include about 0.0050 to about 0.0090 weight percent of the chlorhexidine component, and about 0.10 to about 3.0 weight percent of the propylene glycol component, and about 0.01 to about 0.20 weight percent of the ethylenediaminetetraacetic acid component. According to preferred embodiments, the ophthalmic solutions include up to no more than about 0.0080 weight percent of the chlorhexidine component, and no more than about 2.0 weight percent of the propylene glycol component, and no more than about 0.10 weight percent of the ethylenediaminetetraacetic acid component. In order to minimize potential ocular irritation and in order to ensure adequate anti microbial efficacy, the ophthalmic solutions should have at least about 0.0060 weight percent of the chlorhexidine component, and at least about 0.40 weight percent of the propylene glycol component, and at least about 0.03 weight percent of the ethylenediaminetetraacetic acid component.

In the practice of this invention the optimum amounts of the anti microbial agents may vary among specific ophthalmic solutions. Specific amounts of each anti microbial agent can be readily determined by a person of ordinary skill in the art following testing methods known in the art.

The ophthalmic solutions may also contain various other components including, but not limited to, buffering agents, tonicity adjusting agents, viscosifiers, surfactants, and anti-microbial agents. Furthermore, the solutions preferably have a pH between 6.0and 8. 0.

Any pharmaceutically acceptable buffer system may be utilized in the present invention and include phosphates, borates, acetates and carbonates. Most preferred are the phosphate and borates at total levels of from about 0.1% by weight to about 1.5% by weight of the total composition.

Tonicity adjusting agents refer to those agents that are used to modify the osmolality of an ophthalmic formulation. Examples of useful tonicity agents include, but are not limited to, sodium chloride, potassium chloride, mannitol, sorbitol, glycerin, and mixtures thereof. In one embodiment the tonicity agent is selected from inorganic salts and mixtures thereof. In most applications isotonic (with respect to the ocular environment) solutions are preferred. Osmolalities typically range from about 150 to about 350 mOsm/Kg, but more preferably from about 270 to about 330 mOsm/Kg.

The viscosity of the ophthalmic solutions may be adjusted by adding a viscosifier. Examples of useful viscosity builders include, but are not limited to, hydroxyethylcellulose,hydroxypropylmethylcellulose, carboxymethylcellulose, methyl cellulose, polyvinylpyrrolidone, polyvinylalcohol and mixtures thereof.

In formulating a solution for the treatment of dry eye and ocular discomfort, it may be desirable to include a polysaccharide such as sodium hyaluronate, scleroglucan, xanthan, sodium alginate, keratin sulfate, carrageenan, guarans, pullulan or dextrose.

For contact lens applications it may be desirable to provide a soaking, cleaning and wetting solution. Cleaning agents, such as surfactants, may be included in the ophthalmic solutions and can be anionic, amphoteric, non-ionic or mixtures thereof.

The non-ionic surfactants are preferred due to their lower potential to cause ocular discomfort, such as itching, burning and stinging.

The following examples further illustrate preferred embodiments of the present invention.

EXAMPLE1
The following contact lens solutions were prepared by mixing the components listed in Tablel. The formulation components are given in weight percent, except for chlorhexidine gluconate, which is given in parts per million (ppm), because of the small quantities utilized. The four solutions were prepared to be nearly identical in pH, viscosity and osmolality for comparison purposes.

TABLE I
EMI7.1

INGREDIENT <SEP> A <SEP> B <SEP> C <SEP> D

<tb> Hydroxypropylmethylcellulose* <SEP> 0. <SEP> 60 <SEP> 0. <SEP> 60 <SEP> 0. <SEP> 60 <SEP> 0. <SEP> 60
<tb> Polyvinylalcohol** <SEP> 0. <SEP> 30 <SEP> 0. <SEP> 30 <SEP> 0. <SEP> 30 <SEP> 0. <SEP> 30
<tb> Pluronic <SEP> F127 <SEP> 0. <SEP> 10 <SEP> 0. <SEP> 10 <SEP> 0. <SEP> 10 <SEP> 0. <SEP> 10
<tb> Sodium <SEP> phosphate, <SEP> dibasic <SEP> 0. <SEP> 28 <SEP> 0. <SEP> 28 <SEP> 0. <SEP> 28 <SEP> 0. <SEP> 28
<tb> Potassium <SEP> phosphate, <SEP> monobasic <SEP> 0. <SEP> 055 <SEP> 0. <SEP> 055 <SEP> 0. <SEP> 055 <SEP> 0. <SEP> 055
<tb> Sodium <SEP> chloride <SEP> 0. <SEP> 72 <SEP> 0. <SEP> 40 <SEP> 0. <SEP> 65 <SEP> 0. <SEP> 40
<tb> Propylene <SEP> glycol-0. <SEP> 50-0. <SEP> 50
<tb> Chlorhexidine <SEP> gluconate <SEP> 65 <SEP> ppm <SEP> 65 <SEP> ppm <SEP> 75 <SEP> ppm <SEP> 75 <SEP> ppm
<tb> Disodium <SEP> edetate <SEP> 0. <SEP> 05 <SEP> 0. <SEP> 05 <SEP> 0. <SEP> 05 <SEP> 0. <SEP> 05
<tb> Dionized <SEP> water <SEP> (qs <SEP> to) <SEP> 100 <SEP> 100 <SEP> 100 <SEP> 100
<tb> pH 7.2 7.3 7.2 7.3
Osmolality, mosm/kg 311 273 291 273
Viscosity, cps 47 49 52 54
Appearance clear clear clear clear * Methocel E4M-Dow chemical ** Airvol 325-Air Products
The contact lens solution from Table I were subjected to challenge tests to determine efficacy against various organisms. Samples of each solution were inoculated with the organisms at the concentrations shown in TableII. Viability was tested at various time points following initial incoulation as reported in Tables III, IV,
V andVI.

TABLE II
EMI7.2

<tb> Organism <SEP> Inoculation <SEP> (cfu/ml)
<tb> Staphylococcus <SEP> aureus <SEP> 6538 <SEP> 2.0 <SEP> x <SEP> 106
<tb> Serratia <SEP> marcescens <SEP> 14041 <SEP> 1.1 <SEP> x <SEP> 106
<tb> Pseudomonas <SEP> aeruginosa <SEP> 9027 <SEP> 1. <SEP> 1 <SEP> x <SEP> 106
<tb>
TABLE III
Solution A
EMI8.1

<tb> Organism <SEP> Viability <SEP> (cfu/ml)
<tb> <SEP> 6 <SEP> hours <SEP> 1 <SEP> day <SEP> 7 <SEP> da
<tb> <SEP> s. <SEP> aureus <SEP> 2.8 <SEP> x <SEP> 104 <SEP> < 10 <SEP> < 10
<tb> <SEP> s. <SEP> marcescens <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb> <SEP> .aeruginosa <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb>
TABLE IV
Solution B
EMI8.2

<tb> Organism <SEP> Viability <SEP> (cfu/ml)
<tb> <SEP> 6 <SEP> hours <SEP> 1 <SEP> day <SEP> 7 <SEP> da
<tb> <SEP> s. <SEP> aureus <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb> <SEP> s. <SEP> marcescens <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb> <SEP> : <SEP> aeruginosa <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb>
TABLE V
Solution C

EMI8.3

<tb> <SEP> Organism <SEP> Viability <SEP> (cfu/ml)
<tb> <SEP> 6 <SEP> hours <SEP> 1 <SEP> day <SEP> 7 <SEP> da
<tb> <SEP> s. <SEP> aureus <SEP> 4. <SEP> 7 <SEP> x <SEP> 102 <SEP> < 10 <SEP> < 10
<tb> <SEP> s. <SEP> marcescens <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb> p. <SEP> aeruginosa <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb>
TABLE VI
Solution D
EMI8.4

<tb> <SEP> Organism <SEP> Viability <SEP> (<SEP> (cfu/ml)
<tb> <SEP> 6 <SEP> hours <SEP> 1 <SEP> day <SEP> 7 <SEP> da]
<tb> <SEP> S.aureus <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb> <SEP> s. <SEP> marcescens <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb> p. <SEP> aeruginosa <SEP> < 10 <SEP> < 10 <SEP> < 10
<tb>
The normally recommended disinfecting time for contact lenses is 6 hours of soaking in the disinfecting solution, which roughly correlates to overnight soaking. It would prove instructive to compare the solutions of Table I in their ability to kill staphylococcus aureus, a particularly virulent bacteria, within a six hour period. Table
VII summarizes these results.

TABLE VII
Viability of s. aureus after 6 hours (cfu/ml)
EMI9.1

<tb> Solution <SEP> A <SEP> 2. <SEP> 8 <SEP> x <SEP> 104
<tb> Solution <SEP> B <SEP> < 10
<tb> Solution <SEP> C <SEP> 4. <SEP> 7 <SEP> x <SEP> 102
<tb> Solution <SEP> D <SEP> < 10
<tb>
The data show that use of the ternary preservative system of this invention (Solutions B and D) clearly demonstrate superior disinfecting ability when compared to the conventional preservative system of chlorhexidine and disodium edetate. This is further evidenced when comparing Solution A to Solution D. Simply increasing the chlorhexidine level from 65 ppm to 75 ppm was not as effective as the ternary preservative systems of this invention.

EXAMPLE 2
An in vitro model has been developed to determine the potential for ocular irritation of both ophthalmic solutions and their components. The experimental methods follow the procedure developed by R. Tchao, which is described in"Trans
Epithelial Permeability of Fluorescein In vitro as an Assay to Determine Eye Irritants",
Progress in Vitro Toxicology, Volume 6,1988, pages 271-283 (Mary Ann Liebert, Inc.

Publishers, New York), the disclosure of which is incorporated herein by reference.

The Tchao technique is described as a method of determining potential eye irritation of a substance by correlating damage to a monolayer ofMadin-Darby Canine Kidney (MDCK) cells with damage tocorneal epithelial cells.

The amount of fluorescein passing through the cell monolayer is a function of permeability of the cell mono layer. Higher cell monolayer permeability indicates greater damage to the cell junctions from application of a test solution thereto, whereas lower cell monolayer permeability indicates less severe damage to the cell junctions from application of the test solution. The details of the test are presented below.

Culture preparation: MDCK cells are obtained from ATCC, and maintained in minimum essential medium

(MEM) supplemented with 10% bovine calf serum with iron supplementation (Hyclone, Utah). Stock cultures are passaged weekly using trypsin and EDTA. Cultures are used before passage 50. For the test,0. 5ml of a cell suspension containing 2 x 10 E5 cells are seeded in Millicell HA13mm inserts (Millipore, Bedford, MA). The inserts are placed in 24-well plates and fed with0. 5ml medium. Two days after seeding the cells, the media both inside and outside the inserts are replaced with fresh media. On day 6 after seeding, the inserts are used for testing the solutions. It has been shown that the resistance developed by a confluent MDCK monolayer is about 600ohms/cm2.

Test: Each insert is rinsed with Hanks Balanced Salt Solution (HBSS) 3 x 1 ml using a 10 ml syringe without needle. Each test solution (0.5 ml) is added to the inside of an insert that has been placed in a fresh 24-well plate. Triplicate inserts are used for each test solution. The 24-well plate with inserts and test solutions are placed in a humidified incubator at37 C for 30 minutes. Each series of triplicates is handled sequentially to allow exact timing of the treatment. After incubation, sequentially, each insert is individually rinsed with HBSS 5 x 1 ml using the 10 ml syringe, and is placed in a fresh 24-well plate containing 0.5 ml HBSS in each well. 0.5 ml of a solution of
Na-fluorescein (3 mg/100 ml) is added to each rinsed insert. After incubation at room temperature for 30 minutes, the inserts are sequentially removed from the wells, and the amount of Na-fluorescein in each of the wells is measured in a CytoFluor 2300, using 540 nm excitation and 590 nm emission. For each test, the negative control is HBSS and the positive control is 250pg/ml sodium dodecyl sulfate (SDS). It has been determined that the assay can measure the effect of 50ug/ml SDS, and the effect on the permeability of the monolayer is linearly proportional to the concentrations of SDS from 50-250 g/ml. Fluorescence units (arbitrary) of each test solution is plotted against test solutions.

Interpretation of results: The results are expressed as % of SDS response, and comparisons with the HBSS response. Generally, if the solution is greater than about 20% of the SDS response, the solution may be a mild irritant.

The contact lens solution of Table I were tested in accordance with the above procedure and the following results were obtained.
EMI11.1

<tb>

<SEP> Solution <SEP> Response
<tb> <SEP> SDS <SEP> (250 <SEP> ppm) <SEP> 100
<tb> <SEP> A <SEP> 9. <SEP> 6 <SEP> 0.4
<tb> <SEP> B <SEP> 9. <SEP> 6 <SEP> # <SEP> 0. <SEP> 4
<tb> <SEP> C12. <SEP> 0 <SEP> 0. <SEP> 7
<tb> <SEP> D22 <SEP> 0.7
<tb> HBSS <SEP> 3.7 <SEP> # <SEP> 0.2
<tb>
It can be seen that the solutions tested appear to be non-irritating with the exception of Solution D which may be questionable.

Both Examples 1 and 2 illustrate both the efficacy and safety of the ternary preservative system of this invention.

PRESERVATIVE SYSTEM FOR OPHTHALMIC SOLUTIONS

Claims of **WO0124837**

What is claimed is: 1. An aqueous ophthalmic solution comprising an anti microbially effective amount of a preservative, wherein the preservative system comprises:
(a) chlorhexidine or a water soluble salt thereof ; and
(b) propylene glycol ; and
(c) ethylenediaminetetraacetic acid or a water soluble salt thereof.

2. The solution of Claim 1, wherein component (a) is a water soluble salt of chlorhexidine.

3. The solution of Claim 2, wherein component (a) is chlorhexidine gluconate.

4. The solution of Claim1, wherein component (c) is a water soluble salt of ethylenediaminetetraacetic acid.

5. The contact lens cleaning composition of Claim1, further comprising a viscosity building agent.

6. The solution of Claim 4, wherein component (c) is ethylenediaminetetraacetic acid disodium salt (disodium edetate).

7. The solution of Claim 3, wherein component (c) is ethylenediaminetetraacetic acid disodium salt (disodium edetate).

8. An aqueous solution for treating contact lenses comprising:
(a) about 0.0040 to about 0.0090 weight percent of chlorhexidine or water soluble salt thereof; and
(b) about 0.10 to about 3.0 weight percent of propylene glycol; and 5 (c) about 0.01 to about 0.20 weight percent of ethylenediaminetetraacetic acid or a water soluble salt thereof.

9. The solution of Claim 8, wherein component (a) is chlorhexidine gluconate and component (b) is propylene glycol and component (c) is ethylenediaminetetraacetic acid disodium salt (disodium edetate).

10. The solution of Claim 8, wherein component (a) is present at about 0.0050 to about 0.0080 weight percent and component (b) is present at about 0.30 to about 1.0 weight percent and component (c) is present at about 0.03 to about 0.10 weight percent.

11. The solution of Claim 10, wherein component (a) is present at about 0.0065 weight percent and component (b) is present at about 0.50 weight percent and component (c) is present at about 0.05 weight percent.

12. The solution of Claim 9, further comprising about 0.01 to about 2.5 weight percent of at least one buffering agent.

13. The solution of Claim 8, further comprising at least one viscosity modifier.

14. The solution of Claim 8, further comprising at least one wetting agent.

15. A method of treating a contact lens which comprises treating the lens with an aqueous solution comprising an anti microbially effective amount :
(a) chlorhexidine or a water soluble salt thereof ; and
(b) propylene glycol; and 5 (c) ethylenediaminetetraacetic acid or a water soluble salt thereof.

16. The method of Claim 15, wherein component (a) is a water soluble salt of chlorhexidine and component (b) is propylene glycol and component (c) is a water

soluble salt of ethylenediaminetetraacetic acid.

17. The method of Claim 16, wherein component (a) is chlorhexidine gluconate and component (b) is propylene glycol and component (c) is ethylenediaminetetraacetic acid disodium salt (disodium edetate).

18. The method of Claim 15, wherein the solution comprises:
(a) about 0.0040 to about 0.0090 weight percent of chlorhexidine or water soluble salt thereof ; and
(b) about 0.10 to about 3.0 weight percent of propylene glycol; and 5 (c) about 0.01 to about 0.20 weight percent of ethylenediaminetetraacetic acid or a water soluble salt thereof.

19. The method of Claim 18, wherein component (a) is present at about 0.0050 to about 0.0080 weight percent and component (b) is present at about 0.30 to about 1.0 weight percent and component (c) is present at about 0.03 to about 0.10 weight percent. 20. A method of preserving an ophthalmic solution which comprises including in the solution an anti microbially effective amount of a preservative system consisting essentially of:
(a) chlorhexidine gluconate; and
(b) propylene glycol; and
(c) ethylenediaminetetraacetic acid disodium salt.
